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Appetite and Body Weight Regulation: Is It All in the Brain?

Minireview

Satya P. Kalra
Department of Neuroscience
The University of Florida Brain Institute
University of Florida College of Medicine
Gainesville, Florida 32610

Few human diseases have spurred more public interest recently than obesity and an abnormal rate of body weight gain, the most prevalent nutritional disorders in developed, industrialized nations. Obesity has reached epidemic status since, according to the Institute of Medicine, 59% of Americans are clinically obese or at least 20% above their ideal body weight. This disease is a major contributor to the high rate of morbidity due to increased risk of cardiovascular diseases, including stroke and hypertension, and diabetes. Whereas extraneous causes, such as overeating and/or reduced physical activity, undoubtedly underlie the increased incidence of obesity, the notion that genetic abnormalities are a contributing factor gained an unprecedented boost in the public interest with the cloning of the first major obesity gene (*ob*) and characterization of the protein, leptin, that it encodes (Zhang et al., 1994). The possibility that lack of leptin action in the brain may cause human obesity (Campfield et al., 1995) then provided the wake-up call to the scientific community. Research exploring all aspects of the pathophysiology of obesity and eating disorders, along with new revelations that the brain strives on a minute-to-minute basis to regulate appetite for energy intake necessary for weight regulation (Bray and Ryan, 1996; Kalra and Kalra, 1996; Spiegelman and Flier, 1996), has progressed at a dizzying pace.

All living organisms require food (a nutritional supply) for growth and maintenance. This constant need is met through a highly regulated drive to eat evoked by the sensation of hunger. Because the neural, metabolic, and hormonal signals shown to affect ingestive behavior are generally stable during the period preceding or at the onset of the drive to eat, there is a general consensus that a negative energy balance, such as that provoked by fasting, dieting, or undernourishment, intensifies appetite to prevent underconsumption, but it is unlikely by itself to "trigger" the drive to eat. Recently, a discrete appetite-driving or orexigenic network in the hypothalamus that transduces and releases appetite-stimulating signals, and is tightly programmed by a host of environmental, neural, and metabolic afferent endocrine signals, has been elucidated (Figure 1). While the existence of such a hypothalamic network emitting specific appetite-stimulating neurotransmitters–neuromodulators had been suspected for over 50 years, it was not until the discovery of the potent orexigenic action of neuropeptide Y (NPY; Clark et al., 1984) that understanding this network has become a near reality.

Is NPY a Naturally Occurring Appetite Transducer?

Exogenous NPY administration consistently stimulates feeding under all circumstances and in every vertebrate species studied. Knowing whether the hypothalamic NPY network is a component of the normal–natural appetite transduction pathway is fundamental for understanding the brain's control of appetite and body weight. Evidence in favor of this implication is the abrupt increase in NPY secretion before mealtime in the paraventricular nucleus, one of the sites normally engaged in generating appetite-evoking signals. This heightened secretion of NPY is maintained and appetite is sustained for as long as food is withheld (Kalra et al., 1991). On the other hand, if NPY secretion is halted or its availability at target sites is curtailed experimentally, appetite subsides despite a severe loss in body energy. Furthermore, continuous NPY receptor activation reproduces the normal pattern of intermittent feeding in satiated rats without developing tolerance, and accelerates the rate of body weight gain culminating in obesity that is indistinguishable from that produced experimentally or seen in genetic models (Kalra and Kalra, 1996). Given these results, researchers were surprised to find that a genetic knockout of NPY had no obvious body weight phenotype. However, subsequent experiments have shown genetic interactions of NPY with the product of the *ob* gene (see below), indicating that NPY is an important element in the network (Erickson et al., 1996).

Whereas these demonstrations of temporal and site-specific NPY secretion correlated with onset of the drive to eat suggest that NPY could be a natural appetite transducer, other requisite criteria such as identification of NPY targets have been more elusive. Several attempts, including microinjections and c-fos activation in target cells, have revealed a rather broad field of NPY action within the forebrain (Kalra and Kalra, 1996). The two NPY receptor subtypes that presumably mediate NPY-induced feeding are NPY Y1 and/or a variant Y5 receptor subtype, both of which are widely distributed within and outside the hypothalamus (Larhammar, 1997). The source of NPY that contributes selectively to appetite stimulation is also far from clear. Discrete subpopulations of NPY-producing neurons located locally in the arcuate nucleus (ARC) of the hypothalamus and in remote areas in the brain stem make major projections into NPY-responsive sites in the forebrain. Although only the ARC NPY neurons show fluctuations in preproNPY mRNA levels in fasted and food-restricted rats, this group of neurons cannot be unequivocally designated as the exclusive source of NPY because these fluctuations do not directly correlate with feeding behavior.

Does NPY Act Alone in Brain Regulation of Daily Intake?

Although NPY is the most abundant neuropeptide in the hypothalamus, current morphological and experimental evidence suggests the involvement of an interconnected orexigenic network of NPY, galanin, and opioids in the forebrain (Figure 1). NPY may stimulate food intake on its own and also via stimulation of the release of the other orexigenic peptides, opioids, and galanin (Kalra et al., 1996). As is characteristic of regulated biological

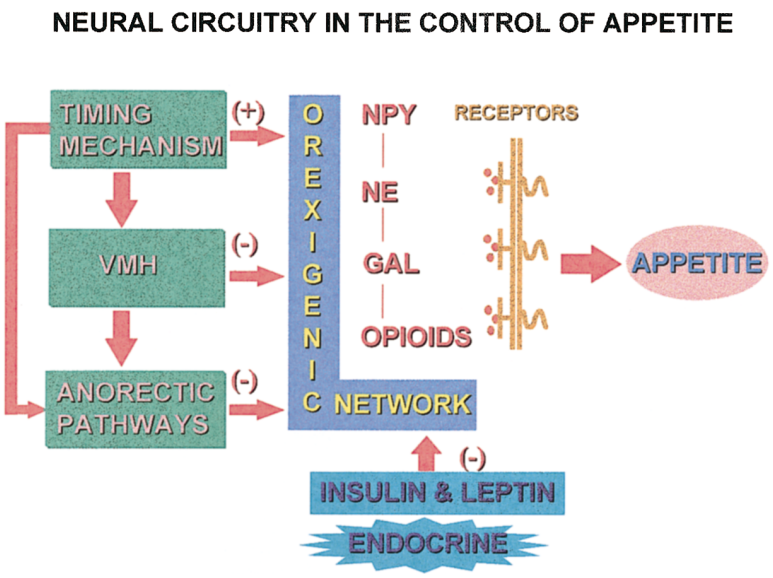

Figure 1. A Schematic Representation of the Various Components of the Brain Neural Circuitry Involved in the Control of Appetite

(+), stimulatory; (−), inhibitory; NPY, Neuropeptide Y; NE, norepinephrine; GAL, galanin; and VMH, ventromedial hypothalamus.

systems, redundancy is evident at another level. Neurotransmitters, such as norepinephrine and γ-aminobutyric acid, coproduced with NPY in the brain stem and the ARC, respectively, stimulate feeding on their own and interact with the NPY-induced response (Horvath et al., 1997). Whether these coexisting signals represent multiple overlapping appetite-stimulating systems or whether they are employed to different extents under different circumstances remains to be determined. That this biological redundancy is vital for energy homeostasis and eventually species' survival is clearly evident in two types of NPY knockout mice. When NPY knockout mice are crossed with the obese (*ob*/*ob*) mouse (Erickson et al., 1996), the double mutant progeny have a body weight closer to normal than the *ob* mutant. This result not only substantiates the importance of the underlying role of NPY, but also strengthened the view that disruption in NPY signaling may contribute to human obesity.

NPY and Body Weight Regulation

Normally, animals rigidly guard their daily body weight around a set point, which is vulnerable to genetic, environmental (quality of macronutrients, energy expenditure, and psychosomatic influence), and hormonal insults. The resultant altered caloric intake may culminate in one of two extremes: excessive body weight gain and obesity, or anorexia and wasting. There is considerable support for the hypothesis that the rigid body weight maintenance is attained through multiple satiety signals that intervene to terminate an ongoing meal and also regulate the intermeal intervals (Bray and Ryan, 1996; Spiegelman and Flier, 1996). Physiologically, this may be relevant, but now it appears that satiety signaling can be overwhelmed by an onslaught of orexigenic signals, especially NPY. Overabundance of NPY produces hyperphagia and abnormal body weight gain (Bray and Ryan, 1996; Kalra et al., 1996). Intriguingly, low abundance of NPY in the hypothalamus, as that produced by lesions in the ventromedial hypothalamus (VMH), also up-regulates appetite to the extent that animals eat equally throughout the day, both during the lights-on period when there is normally little feeding activity, and during the lights-off period of normally robust eating. Seemingly, marked diminution of NPY availability at target sites results in the development of supersensitivity to NPY so that amounts of exogenous NPY that are insufficient to evoke feeding in normal rats stimulate a near normal drive for food. Thus, one can picture a vicious circle of internal and external environmental factors that result in loss of the tight control on NPY neurosecretion causing either overabundance or low abundance, both of which cause exaggerated and unregulated eating patterns and increased body weight. This revelation may partly account for the difficulties faced by physicians in designing therapies to decrease the body weight of obese patients.

If the orexigenic network generates a powerful behavioral drive, then two basic questions arise: what orchestrates dissipation of appetite to terminate the ongoing feeding, and are there signals that tonically restrain orexigenic signals during the intermeal interval? Neither of these two questions has been specifically addressed. Since lesions in the lateral hypothalamus produce inanition and wasting attributable to a lack of motivational drive to eat (Bray and Ryan, 1996), it comes as no surprise that organisms have designed more than one way to address these questions. Interestingly, as with the trigger for appetite, both termination and tonic restraint of eating behavior may be chemically addressed, encompassing both the neural and hormonal pathways. In the forebrain, a spectrum of locally produced neuromodulators can inhibit intake in various experimental paradigms. It is possible that some of these may represent the physiologically relevant "off" switches. Unlike cholecystokinin, a well-studied putative satiety signal, several of these anorectic neuromodulators seem to exert their anti-appetite effects largely through interruption of NPY efflux and action at postsynaptic levels within the hypothalamus. This list includes peptide members of the corticotropin-releasing factor family (Spina et al., 1996), glucagon-like peptide-1 (Turton et al., 1996), me-

lanocyte-stimulating hormone acting through melanocortin-4 receptors (Fan et al., 1997), and serotonin interfering drugs, such as d-fenfluramine, the active component of the currently in-vogue diet pill Redux, and the other serotonin reuptake blocker, fluoxitine (Kalra and Kalra, 1996). One can now add to this list the cytokines, such as ciliary neurotrophic factor, an endogenous anorectic and cachectic agent during infection and disease that acts by blocking NPY synthesis, release, and postsynaptic action (Kalra et al., 1996, Soc. Neurosci. abstract).

The amount of body fat can be regulated by various peripheral hormonal signals. One of these, pancreatic insulin, acts via the hypothalamus to control appetite and energy expenditure (Bray and Ryan, 1996; Spiegelman and Flier, 1996). This large circulating protein is transported across the blood–brain barrier endothelium into the cerebrospinal fluid by an active process, and one of the central sites of its action to suppress feeding is the paraventricular nucleus (Kalra and Kalra, 1996). Insulin suppresses NPY release from the nerve terminals rapidly enough to support the possibility that the postprandial rise in insulin may terminate NPY-dependent eating episodes. However, the efficacy of insulin as the primary hormonal signal in body weight control has been questioned because of the fact that hyperinsulinemia generally accompanies hyperphagia and obesity in man and experimental models.

The "lipostat" hypothesis has been an enduring proposal to explain the tight control on body weight (Zhang et al., 1994; Spiegelman and Flier, 1996). It predicts that secretions from fat cells may be the key signals to the brain to regulate feeding and body fat deposition. One of these secretory products is encoded by the recently cloned mouse *obese* (*ob*) gene and its counterparts in other species, including humans (Zhang et al., 1994). This identification was followed in quick succession by characterization of 16-kd protein, leptin (Leptos = thin), establishing its efficacy in normalizing body weight and appetite in leptin-deficient ob/ob mice by systemic and central injections (Campfield et al., 1995; Spiegelman and Flier, 1996), and most recently cloning of its receptor (Tartaglia et al., 1995). The leptin receptor (OB-R), a product of the *db* gene, which has been long believed to encode the receptor for a weight-controlling hormone, is expressed as various splice variants in the rodent and human hypothalamus (Considine et al., 1996a; Lee et al., 1996; Mercer et al., 1996).

Significant new insights into the relationship between peripheral signals, insulin, and leptin, and their impact on the orexigenic network (Figure 1) have provided some critical missing pieces in the "lipostat" puzzle. Insulin up-regulates leptin synthesis and release from adipocytes, and leptin has been shown to cross the blood–brain barrier via the parenchymal compartment (Bray and Ryan, 1996; Spiegelman et al., 1996). An important central action of leptin is likely to be inhibition of NPY release and synthesis in the ARC of the hypothalamus and possibly inhibition of the postsynaptic appetite-stimulating effects of NPY (Stephens et al., 1995). The findings that insulin and leptin each inhibit NPY release and that insulin has the potential to up-regulate leptin output together support the likelihood that these two hormonal signals are key components of the long-sought peripheral negative feedback link that acts through a central orexigenic network for weight control (Figure 1).

Whereas this identification of putative key facets of the "lipostat" theory generated an immediate all-round excitement, further validation through analysis of circulating levels of leptin in rodents and humans has been less than encouraging. Contrary to expectations, circulating leptin levels are generally at their lowest during the intermeal intervals and rise either as part of the innate daily rhythm or long after initiation of intake. Furthermore, a strong positive correlation between plasma leptin levels and body fat mass has been found, suggesting that leptin production is regulated by the mass of adipocytes. The fact that circulating levels are highly variable among individuals and are either in the normal range or elevated in obese individuals argues against the leptin-deficiency hypothesis as the cause of unregulated eating and obesity in most cases (Spiegelman and Flier, 1996; Considine et al., 1996a, 1996b; Maffei et al., 1996). It is possible that defective transport to the central nervous system, extremely rapid development of resistance, and/or tolerance to the action of leptin in the hypothalamus may be common in obese individuals. Further, unlike the receptor variants detected in diabetic, obese *db*/*db* mice, the OB-R appears to be no different in eight obese and lean individuals examined so far (Considine et al., 1996a), giving rise to the idea of a defective postreceptor downstream leptin signal transduction underlying the hypothalamic insensitivity to leptin.

The VMH lesion-induced rodent obesity model provides clues to this puzzle of high leptin production concomitant with unregulated phagia and excessive rate of body weight gain (Dube et al., 1996, Soc. Neurosci. abstract). Soon after the production of chemical lesions with no apparent structural damage in the VMH and after electrolytic lesions in the VMH, leptin production is exaggerated concomitant with reduced availability of NPY in the paraventricular nucleus and loss of the regulated daily pattern of feeding (Spiegelman and Flier, 1996; Dube et al., 1996, Soc. Neurosci. abstract; Kalra et al., 1996). The resultant hyperphagia and steady gain in weight, as mentioned above, may be a consequence of rapid development of NPY receptor supersensitivity (Figure 1; Dube et al., 1996, Soc. Neurosci. abstract; Kalra et al., 1996). Thus, thorough examination of the cellular and molecular bases of the shifts in receptor dynamics of orexigenic signals accompanying weight disorders is warranted.

Notwithstanding these complexities, a neural timing mechanism also operates upstream from the orexigenic network in the daily management of energy homeostasis (Figure 1). Although the precise anatomical boundaries are not clearly defined, this device is likely to be composed of a group of neurons that integrate incoming internal and external environmental information for the timely onset of the drive to eat. Whether this network operates independently as evident in primates, or whether it is entrained to the circadian timekeeper, the hypothalamic suprachiasmatic nucleus, as in most other mammals, remains to be ascertained. Intriguingly,

the VMH has also been suspected as an integrated constituent of the timing mechanism because neural damage at this site, as that seen after destruction of the suprachiasmatic nuclei (Nagai et al., 1978), results in loss of regulated feeding.

A distinct neural circuitry in the brain is clearly involved in the control of appetite and body weight gain (Figure 1). At least four basic elements of this circuitry have been deciphered, with only the NPYergic component of the orexigenic network as the target for peripheral hormones to exert a regulatory tonic restraint on NPY secretion. Consequently, the important task ahead is to trace the signal transfer pathways among the three interactive circuits that mediate the escape from the inhibitory influence of the VMH and/or anorectic signals for the release of orexigenic signals. Additionally, new revelations that both over- and underexpression of hypothalamic NPY result in unregulated eating and body weight gain, in conjunction with resistance to insulin and leptin, underscore a new rationale for designing therapeutic strategies to control appetite and body weight. Seemingly, the efficacy of anti-appetite drugs will depend both on their effectiveness to curtail the availability of orexigenic messenger molecules at the target sites while preventing the development of receptor supersensitivity.

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